Remarks

The Office Action mailed 2 October 2003 has been received and reviewed. Claims 1, 10, 12, 14, 16, 18, 19, 23, 25, 26, 28, and 30 having been amended, and claims 20, 22 and 31 having been canceled, the pending claims are claims 1-19, 21, 23-30, and 32-34. Reconsideration and withdrawal of the rejections are respectfully requested.

The amendment of claims 1, 19, 23, and 25 is supported by the specification at, for instance, page 20, line 23 through page 21, line 2.

The amendment of claims 10, 12, and 26 corrects clerical errors.

The amendment of claims 14 and 30 is supported by the specification at, for instance, page 18, lines 27-31.

The amendments of claim 18 are supported by the specification at, for instance, page 18, lines 27-31, and by claim 20 as originally filed.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 22-28 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The cancellation of claim 22, and the amendment of claim 23 and 25 renders the present rejection moot with respect to those claims and the claims dependent thereon. In claim 28, the recitation of "a second section marker" is amended to recite "a second selection marker."

The Examiner is requested to reconsider and withdraw the rejection of claims 22-28 under 35 U.S.C. §112, second paragraph.

The First 35 U.S.C. §103 Rejection

The Examiner maintained the rejection of claims 1-13, 23-29, 31 and 34 under 35 U.S.C. §103(a) as being unpatentable over Ho et al. (WO95/13362) in view of Hallborn et al. (Canadian Patent No. 2,090,122). Applicants note with appreciation the withdrawal of this rejection with respect to claims 14-22, 30, and 32-33, and respectfully maintain the traversal of

this rejection with respect to the remaining claims. In addition to the remarks made by the applicant in the prior response, the Examiner is requested to consider the following comments.

In the comments at paragraph 8 of the Action, the Examiner notes that "claim 1 does not require the introduction of a gene encoding xylulokinase . . . ." It is true that claim 1 does not recite the introduction of a gene encoding xylulokinase; however, to arrive at the yeast of claim 1 the skilled person would introduce a gene encoding xylulokinase. Thus, when analyzing the cited documents in combination with each other (see Response mailed June 27, 2003, pages 8-9, first and second full paragraphs), it is appropriate to include a discussion of how Ho et al. and Hallborn et al. arrive at the yeasts they disclose.

In the comments at paragraph 8 of the Action, the Examiner also notes that "applicants statements acknowledges that the reference teaches a functioning xylulokinase gene." Applicants agree, but the Examiner is requested to note that the functioning xylulokinase gene of Hallborn et al. is present in the yeast at its normal location, i.e., a specific site in one of the yeast chromosomes. The functioning xylulokinase gene of Ho et al. is present in its normal location in one of the yeast chromosomes and on the non-integrative plasmid disclosed in Ho et al. However, claim 1 recites "genes integrated at multiple reiterated ribosomal DNA sites of the yeast, said genes encoding . . . xylulokinase" and claims 23 and 25 recite "multiple copies of exogenous DNA integrated into chromosomal DNA of the yeast, the exogenous DNA including genes encoding . . . xylulokinase." Ho et al. and Hallborn et al. may teach functioning xylulokinase genes, but they do not teach or suggest a yeast with a xylulokinase gene integrated at multiple reiterated ribosomal DNA sites of the yeast.

The Action notes that there is motivation to combine because "both references teach the fermentation of xylose to ethanol and the use of the claimed enzymes" (Action, paragraph 8) and "because Ho et al. disclose that ethanol is an ideal liquid fuel for automobiles and Hallborn et al. disclose a method to perform stable transformations over time" (Action, paragraph 7). Applicants have detailed the reasons why there is no motivation to combine the cited documents in the Response mailed June 27, 2003 (see page 9, first two full paragraphs), but the reasons raised in the Response have not been addressed by the Examiner. Specifically, the

Examiner has not addressed why a skilled person would be motivated to combine Ho et al. with Hallborn et al. when doing so would result in modifying the vectors of Ho et al. to no longer include a gene encoding xylulokinase, and Ho et al. teach that a gene encoding xylulokinase is required. Likewise, the Examiner has not addressed why a skilled person would be motivated to combine Hallborn et al. with Ho et al. when doing so would result in the yeast of Hallborn et al. also containing an introduced gene encoding xylulokinase, and Hallborn et al. teach that the recipient yeast already have a functioning xylulokinase gene. "The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done" (MPEP §706.02(j), emphasis added). Moreover, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP §2143.01 (emphasis added). The Examiner is respectfully requested to address applicants' arguments on why the skilled person would not be motivated to combine the cited documents.

The Examiner also asserts that Applicants present inconsistent and contradictory arguments regarding the assertion that none of the cited documents teach the product plasmid vector. The Examiner is respectfully requested to consider the following comments on the teachings of the cited documents regarding the product plasmid vector. Hallborn et al. teach the introduction of two separate DNAs; the *first* is a DNA fragment that is integrated, the *second* is an autonomously replicating plasmid that does not integrate (see the Response mailed June 27, 2003, at page 8, first paragraph). The purpose of the autonomously replicating plasmid was to permit identification of transformants. The autonomously replicating plasmid did not contain any exogenous DNA that was integrated in the chromosomal DNA of the target yeast, and it was later removed from the cells (see Hallborn et al. at page 7, lines 27-31, and page 17, lines 24-30). Thus, none of the cited documents teach or suggest a plasmid vector containing a functional yeast autonomous replicating sequence *and an exogenous DNA* for use in integrating the exogenous DNA sequence into chromosomal DNA of a target yeast cell (claims 28, 29, and 34).

For these reasons and the arguments already of record, Applicants respectfully request reconsideration and withdrawal of the present rejection of claims 1-13, 23-29, 31 and 34 under 35 U.S.C. §103(a) in view of the cited documents.

The Second 35 U.S.C. §103 Rejection

The Examiner maintained the rejection of claims 1-34 under 35 U.S.C. 103(a) as obvious over Ho et al. (WO 95/13362) in view of Lopes et al. (*Yeast* 1996;12(5):467-77). Applicants respectfully maintain the traversal of this rejection. In addition to the remarks made by the applicant in the prior response, the Examiner is requested to consider the following comments.

In the comments at paragraph 9, page 8, of the Action, the Examiner states that "[m]ultiple copies of the plasmid were successfully integrated into the genome (over 140 copies); which are stably maintained in non-selective medium for multiple generations over long periods of time (see abstract and pages 467-475)." The Examiner's statement appears to refer to a sentence at col. 2 of page 467, of Lopes et al., but this statement in Lopes et al. cites a separate document that is not part of the present rejection. "Where a reference is relied on to support a rejection, whether or not in a minor capacity, that reference should be positively included in the statement of the rejection." See *In re Hoch*, 428 F.2d 1341, 1342 n.3 166 USPQ 406, 407 n. 3 (CCPA 1970), MPEP §706.02(j). If this statement by the Examiner is part of the rejection, the Examiner is respectfully requested to positively include this document in the rejection.

Moreover, Lopes et al. state that "[i]n this paper we describe studies aimed at establishing whether pMIRY-type plasmids can indeed be stably maintained under the conditions applied during industrial production of proteins" (page 467, col. 2), and Lopes et al. go on to clearly prove that the pMIRY-type plasmids are *not* stably maintained under certain conditions. Lopes et al. disclose that "[s]table maintenance is only observed when the complete plasmid has a size no larger than that of the rDNA unit (9.1 kb)" (abstract, also see page 473, col. 2. for a similar statement); that "plasmid size is a crucial factor in determining mitotic stability of the pMIRY-type vectors" (page 473, col. 2); and "the mitotic stability of pMIRY2 vectors

carrying such a [foreign] gene is decreased significantly" and yeast transformed with such a vector "lose some 80% of their vector copies over a period of 70 generations of growth in non-selective medium containing galactose as the sole carbon source" (page 472, col. 2). Thus, the Lopes et al. document that has been cited in this rejection does *not* teach that integrated plasmids are stably maintained in non-selective medium for multiple generations over long periods of time.

Applicants respectfully submit that the skilled worker would not be motivated by reading Ho et al. to combine the disclosure of Ho et al. with the disclosure of Lopes et al. to yield the present claims, and the skilled worker would not be motivated by reading Lopes et al. to combine the method of Lopes et al. with the method of Ho et al. to yield the present claims. Combining Ho et al. with Lopes et al. would result in the pMIRY-type vectors of Lopes et al. modified to contain the genes encoding xylose reductase, xylitol dehydrogenase, and xylulokinase of Ho et al. Addition of the genes encoding xylose reductase, xylitol dehydrogenase, and xylulokinase to the smallest pMIRY vector of Lopes et al. would result in a vector of at least 11 kb (see Response mailed June 27, 2003 at page 12, first full paragraph, for explanation of how such a vector would be 11 kb). Lopes et al. disclose that "[s]table maintenance is only observed when the complete plasmid has a size no larger than that of the rDNA unit (9.1 kb)" (abstract, also see page 473, col. 2, for a similar statement). Thus, the vector made by combining the two documents would not be stably maintained. Independent claims 1, 19, 23, and 25 are directed to a yeast containing integrated genes encoding xylose reductase, xylitol dehydrogenase, and xylulokinase, and the fermentation activity is not decreased after culture in non-selective medium for greater than 40 generations. Since the vector made by combining the two documents would not be stably maintained, the skilled worker would not be motivated to combine Ho et al. and Lopes et al. to make the yeast of independent claim 1, 19, 23, or 25, or practice the method of claim 18.

Applicants submit that even if the cited documents were combined, there would be no reasonable expectation of success. For instance, the independent method claims 14, 18, and 30 recite, inter alia, "repeatedly replicating the cells from step (a) to produce a number of

generations of progeny cells while selecting for cells which include the selection marker, promoting the retention of the replicative and integrative plasmid in subsequent generations of the progeny cells and produce progeny cells having multiple integrated copies of the exogenous DNA" (claim 14), "repeatedly replicating the transformed yeast cells from step (i) to produce a number of generations of progeny cells while selecting for cells which include the selection marker, so as to promote the retention of the replicative plasmid in subsequent generations of the progeny cells and result in progeny cells each containing multiple integrated copies of the exogenous DNA" (claim 18), and "replicating cells having reiterated genomic DNA and which contain a replicative and integrative plasmid comprising a yeast autonomous replicating sequence and containing the exogenous DNA to produce multiple generations of progeny cells while selecting for cells which include the selection marker, so as to promote the retention of the replicative and integrative plasmid in subsequent generations of the progeny cells and produce progeny cells having multiple integrated copies of the exogenous DNA" (claim 30). Even if Ho et al. and Lopes et al. were combined, the plasmids produced by such a combination would not result in producing progeny cells having multiple integrated copies of the exogenous DNA after repeatedly replicating those cells receiving the plasmid.

Moreover, to establish a prima facie case of obviousness, the combined teachings must teach or suggest each and every limitation of the claimed invention (MPEP § 2143). It is respectfully submitted that the combined teachings of the two cited documents do not teach or suggest each and every element of independent claims 14, 18, 28, 29, 30, and 34.

Method claims (independent claims 14, 18, and 30). The method claims recite, inter alia, "transforming the cells with a replicative and integrative plasmid comprising a yeast autonomous replicating sequence, exogenous DNA, and a first selection marker" (claim 14), "'transforming yeast cells with a replicative and integrative plasmid comprising a yeast autonomous replicating sequence, exogenous DNA . . . and a selection marker" (claim 18), and "replicating cells having reiterated genomic DNA and which contain a replicative and integrative plasmid comprising a yeast autonomous replicating sequence and containing the exogenous DNA " (claim 30). Ho et al. and Lopes et al. do not teach or suggest the use of a replicative and

integrative plasmid comprising a yeast autonomous replicating sequence that also contains the exogenous DNA. Since none of the cited documents teach or suggest the methods of claims 14, 18, or 30 that include the use of a replicative and integrative plasmid containing a yeast autonomous replicating sequence and exogenous DNA, the cited documents do not teach or suggest each and every element of claims 14, 18, and 30.

Product (vector) claims (independent claims 28, 29, and 34). None of the cited documents teach or suggest a "plasmid vector comprising a functional yeast autonomous replicating sequence and an exogenous DNA . . . the plasmid vector for use in integrating the exogenous DNA sequence into chromosomal DNA of a target yeast cell" (claim 28), a "plasmid vector comprising a functional yeast autonomous replicating sequence and exogenous DNA . . . the plasmid vector for use in integrating the exogenous DNA sequence into chromosomal DNA of a yeast to form stable integrants which ferment xylose to ethanol" (claim 29), or a "plasmid vector comprising a functional yeast autonomous replicating sequence and exogenous DNA . . . the plasmid vector for use in integrating an exogenous DNA sequence into chromosomal DNA of a target yeast cell" (claim 34). None of the cited documents teach or suggest a plasmid vector containing a functional yeast autonomous replicating sequence and an exogenous DNA for use in integrating an exogenous DNA sequence into chromosomal DNA of a target yeast cell. Thus, the cited documents do not teach or suggest each and every element of claims 28, 29, and 34.

Summary

It is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 27 day of January, 2004, at 1:30pm (Central Time).

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